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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,791	11/12/2003	Christopher William Aston	WYE-076	8289

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EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/706,791	ASTON ET AL.	
	Examiner	Art Unit	
	Frank W. Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-27 and 32-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-27 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2004* is/are: a)☒ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on September 15, 2006 has been entered. The claims pending in this application are claims 23-34. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the response filed on September 15, 2006.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. New Matter

Claims 23-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The recitation "the composition has a greater affinity for IGFBP-2 than for IGFBP-1, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6" is added to the newly amended independent claim 23. Although the specification describes that dose-dependent inhibition of ^{125}I IGF-I binding to IGFBP-1 to IGFBP-6 by IGF-I and NBI-31772 (see Figure 8 and Example 8 in pages 61 and 61 of the specification), examples 2, 3, and 8 of the specification as suggested by applicant fails

to define or provide any disclosure to support such claim recitation because a pharmaceutical composition recited in claim 23 is read as any kind of pharmaceutical composition which dissociates a protein complex comprising an Insulin-like growth factor (IGF) and an Insulin-like growth factor binding protein-2 (IGFBP-2), and is not limited to IGF-I or NBI-31772 and can be read as something else which is not IGF-I or NBI-31772. Note that, although example 8 of the specification cites papers from Liu *et al.,* (J. Biol Chem., 276:32419-32422, 2001) and Chen *et al.,* (Journal of Medicinal Chemistry, 44(23), 4001-4010, 2001), which teach the effects of NBI-31772 on binding of IGF-I to IGFBPs, since the specification does not incorporate these papers by references, the papers from Liu *et al.,* and Chen *et al.,* are not considered as a part of the specification.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added).

4. Enablement

Claims 23-27 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

To begin, there is no direction or guidance in the specification to show that a composition which dissociates a protein complex comprising an insulin-like growth factor (IGF) and insulin-like growth factor binding protein-2 (IGFBP-2) can be used as a pharmaceutical composition wherein the composition has a greater affinity for IGFBP-2 than for IGFBP-1, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6 as recited in claims 23-27 and a composition which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP) can be used as a pharmaceutical composition wherein the composition is a small molecule as recited in claims 32-34. While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether a composition which dissociates a protein complex comprising an insulin-like growth factor (IGF) and insulin-like growth factor binding protein-2 (IGFBP-2) can be used as a pharmaceutical composition wherein the composition has a greater affinity for IGFBP-2 than for IGFBP-1, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6 and whether a composition which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein

(IGFBP) can be used as a pharmaceutical composition wherein the composition is a small molecule.

Claims 23-27 is directed to a pharmaceutical composition which dissociates a protein complex comprising an insulin-like growth factor (IGF) and insulin-like growth factor binding protein-2 (IGFBP-2) wherein the composition has a greater affinity for IGFBP-2 than for IGFBP-1, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6 while claims 32-34 are directed to a pharmaceutical composition which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP) can be used as a pharmaceutical composition wherein the composition is a small molecule. A pharmaceutical composition is read as a composition used for the purpose of treating a disease. However, the specification does not show that the compositions recited in claims 23-27 and 32-34 can be used for treating any kind of disease. In view of claims 23-27 and 32-34, it is unclear how the compositions recited in claims 23-27 and 32-34 can served as a pharmaceutical composition.

With above unpredictable factor, the skilled artisan will have no way to predict the experimental results. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. The undue experimentation at least includes to test whether the composition recited in claims 23-27 and 32-34 can be used for treating any kind of disease so that such composition can served as a pharmaceutical composition.

Response to Arguments

I. In page 5, first paragraph bridging to page 6, first paragraph of applicant's remarks, applicant argues that: (1) "[A]pplicants submit that the application does indeed enable pharmaceutical compositions. The application discusses in some detail (see, for example, pages

51-54) how to formulate and administer pharmaceutical compositions. Thus, the application teaches how to make and how to use the claimed invention. This is sufficient to comply with the enablement requirement of 35 U.S.C. § 112; Applicants therefore request that the rejection be reconsidered and withdrawn"; and (2) "Applicants understand that the Office action questions whether the pharmaceutical composition would in fact be useful to treat any disease. The application, however, reports that IGFs are therapeutically useful (see, e.g., the experiment disclosed at page 64 of the application; see also page 5 of the application, discussing the efficacy of IGF-I with respect to hypoxic-ischemic brain injury and age-related changes in NMDA receptor subtype and the age-related decline in both working and reference memory and cell proliferation in the dentate gyrus). The present application demonstrates the elevation of IGFBP-2 gene expression in fibroblasts from subjects with major depression (Example 2); the slight elevation of IGFBP-2 gene expression in brain tissue from subjects with major depression (Example 3); and the effects on IGFBP-2 gene expression of drugs possessing anxiolytic and antidepressant properties (Example 6). Applicants submit that, based on the high level of skill in the art, the specific guidance in the application and the knowledge in the art, any experimentation to confirm the effectiveness of the disclosed and enabled pharmaceutical compositions of the invention which dissociate an IGF from an IGFBP such as IGFBP2 would be routine and not undue".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since pages 51-54 of the specification suggested by applicant only shows possible components for a pharmaceutical composition and possible uses and does not show that the pharmaceutical composition recited in claims 23-27 and 32-34 can be used for

treating a disease, it is unclear how the composition recited in claims 23-27 and 32-34 can be considered as a pharmaceutical composition. Second, pages 5 and 64 of the specification do not teach the efficacy of IGF-I with respect to hypoxic-ischemic brain injury and age-related changes in NMDA receptor subtype and the age-related decline in both working and reference memory as argued by applicant. Third, although examples 2 and 3 (see pages 54 and 55 of the specification) show the elevation of IGFBP-2 gene expression in fibroblasts from subjects with major depression and the slight elevation of IGFBP-2 gene expression in brain tissue from subjects with major depression, examples 2 and 3 do not show that the pharmaceutical composition recited in claims 23-27 and 32-34 can be used for treating a disease. Fourth, although example 6 (see page 57 of the specification) shows that the some drugs possessing anxiolytic and antidepressant properties can alter IGFBP-2 gene expression, example 6 does not show that these drugs possessing anxiolytic and antidepressant properties alter IGFBP-2 gene expression by dissociating a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP) so that these drugs can be used as the pharmaceutical composition as recited in claims 23-27 and 32-34. Therefore, claims 23-27 are not enable.

II. In page 7, second paragraph of applicant's remarks, applicant argues that "[A]pplicants also note that the enablement of the present application was confirmed by a paper published after the priority date of the present application and before the actual filing date of the present application. Applicants enclose as IDS reference C1 a copy of Mackay et al. (2003 Oct) J. Cereb. Blood Flow Metab. 23(10): 1160-7, reporting that 'administration of NBI-31772 at the time of ischemia onset also dose-dependently reduced infarct size, and the highest dose (100 microg) significantly reduced both total (by 40%, $P<0.01$) and cortical (by 43%, $P<0.05$) infarct volume'

in one model and, in another model 'reduced both cortical infarct volume (by 40%, P<0.01) and brain swelling (by 24%, P<0.05), and it was still effective when treatment was delayed up to 3 hours after the induction of ischemia'(Mackay, abstract)".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Although Mackay *et al.,* teach neuroprotective effects of NBI-31772 *in vitro* and *in vivo*, since claims 23-27 are directed to any kid of pharmaceutical composition which dissociates a protein complex comprising an insulin-like growth factor (IGF) and insulin-like growth factor binding protein-2 (IGFBP-2) wherein the composition has a greater affinity for IGFBP-2 than for IGFBP-1, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6 while claims 32-34 are directed to any kind of pharmaceutical composition which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP) wherein the composition is a small molecule, and the pharmaceutical compositions recited in claims 23-27 and 32-34 are not limited to NBI-31772 as taught by Mackay *et al.,* and argued by applicant.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 23-27 and 32-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu *et al.,* (The Journal of Biological Chemistry, 35, 32419-32422, August 2001).

Regarding claims 23, 24, 26, 32, and 33, since Liu *et al.,* teach that ki for binding of NBI31772 to IGFBP-2 is 1.18±0.27 nM and NBI31772 can inhibit the binding of ^{125}I IGF-I binding to IGFBP-2 (see Figure 2 and Table II in page 32421), Liu *et al.,* disclose a pharmaceutical composition (ie., NBI-31772) which dissociates a protein complex comprising an insulin-like growth factor (IGF) and insulin-like growth factor binding protein-2 (IGFBP-2), wherein the composition has a greater affinity for IGFBP-2 (ie., ki for binding of NBI-31772 to IGFBP-2 is 1.18±0.27 nM) than for IGFBP-1, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6 (ki for binding of NBI-31772 to IGFBP-1, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6 are 3.36±1.82 nM, 5.64±0.47 nM, 1.54±0.54 nM, 3.90±1.00 nM, and 16.60±6.10 nM respectively) as recited in claim 23 and a pharmaceutical composition (ie., NBI-31772) which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP) (ie., IGFBP-2) wherein the composition is a small molecule (ie., NBI-31772 with molecular weight of 315 Da) as recited in claims 26 and 32 wherein the protein complex is further defined as a dimeric complex comprising IGF and IGFBP-2 as recited in claim 24, the protein complex is further defined as a dimeric complex comprising IGF and IGFBP as recited in claim 33.

Regarding claims 25 and 34, since claim 23 and 32 are directed to a pharmaceutical composition which dissociates a protein complex comprising an insulin-like growth factor (IGF) and an insulin-like growth factor binding protein (IGFBP) or insulin-like growth factor binding protein-2 (IGFBP-2) and the protein complex are not a part of structural limitations of claims 23

and 32, and NBI-31772 taught by Liu *et al.*, has an ability to dissociates a protein complex comprising an IGF and an IGFBP or IGFBP-2 and ALS, Liu *et al.*, disclose the protein complex further comprises an acid labile subunit (ALS), wherein the ration of IGF to IGFBP-2 to ALS is 1:1:1 as recited in claim 25 and the protein complex further comprises an acid labile subunit (ALS), wherein the ration of IGF to IGFBP to ALS is 1:1:1 as recited in claim 34.

Regarding claim 27, since Liu *et al.*, teach that ki for binding of unlabeled hIGF-1 to IGFBP-2 is 0.06±0.02 nM, the unlabeled hIGF-1 can inhibit the binding of ^{125}I IGF-I binding to IGFBP-2, and has a greater affinity for IGFBP-2 (ie., ki for binding of hIGF-1 to IGFBP-2 is0.06±0.02 nM) than for IGFBP-1, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6 (ki for binding of NBI-31772 to IGFBP-1, IGFBP-3, IGFBP-4, IGFBP-5, and IGFBP-6 are 0.12±0.03 nM, 0.21±0.04 nM, 0.10±0.03 nM, 0.22±0.04nM, and 2.71±0.04 nM respectively) (see Figure 2 and Table II in page 32421), Liu *et al.*, disclose that the composition is a peptide (ie., the unlabeled hIGF-1) as recited in claim 27.

Therefore, Liu *et al.*, teach all limitations recited in claims 23-27 and 32-34.

7. Claims 32-34 are rejected under 35 U.S.C. 102(e) as being anticipated by Sakano *et al.*, (US Patent No. 6,428,781 B1, priority date: December 26, 1997) as evidence by Li *et al.*, (US Patent No. 5,650,295, published on July 22, 1997).

Regarding claims 32-34, since Li *et al.*, teach that a small molecule is a peptide (see column 10, lines 60-65), Sakano *et al.*, as evidence by Li *et al.*, teach a pharmaceutical composition (ie., [Leu27, Leu43]rIGF-II) which dissociates a protein complex comprising an Insulin-like growth factor (IGF) and an Insulin-like growth factor binding protein (IGFBP)

wherein the composition is a small molecule (ie., [Leu27, Leu43]rIGF-II) as recited in claim 32 and the protein complex is further defined as a dimeric complex comprising IGF and IGFBP (ie., a complex formed by IGF and IGFBP) as recited in claim 33 or the protein complex further comprises an acid labile subunit (ALS) and the ratio of IGF to IGFBP to ALS is 1:1:1 (ie., a ternary complex formed by IGF, IGFBP, and ALS) as recited in claim 34 (see columns 9 and 10, Examples 16 and 17 in columns 21, and Figures 16 and 17).

Therefore, Sakano *et al.,* as evidence by Li *et al.,* teach all limitations recited in claims 32-34.

Response to Arguments

In page 6, fourth paragraph bridging to page 7, second paragraph of applicant's remarks, applicant argues that Sakano *et al.,* do not teach claims 32-34 since [Leu27, Leu43]rIGF-II is not a small molecule in view of Schreiber (2005) Nature Chemical Biol. 1(2):64-66 and definition for small molecule therapeutics.

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, since Li *et al.,* teach that a small molecule is a peptide (see column 10, lines 60-65) and [Leu27, Leu43]rIGF-II taught by Sakano *et al.,* is a peptide, and the claims does not require that a small molecule is not a peptide, there is no definition for "small molecule" in the specification, and the word "small" is a relative term, [Leu27, Leu43]rIGF-II is considered as a small molecule in the rejection. Second, since the claims do not require that a small molecule is used therapeutically, the definition for "small molecule therapeutics" argued by applicant cannot be used to define the small molecule recited in claim 32.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. No claim is allowed.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

November 15, 2006

FRANK LU
PRIMARY EXAMINER